CGATGTCTGCACAAGGCTGTCACTCAGGTGGCAGTGGCTGACACGTGGCCGGGCAGCTCTGC
TGCTGCGGCGCGAAGTCGAGAGGCGGCGGGGTCCGTGGCGCGCGCTCGCATTGCTCCGAGGC
TCCGAGCGGCGATACGGGCGGGCGCCGACGGCAGGGTCTCCATGCCCGCGCGTGGGGCGGGC
CGCTGATGGAGCGCGCCACCCGGCCCGGGCCGCGCGCGCTGCTGCTGCTTCTGTTCCTGCTG
CTGGGCTGCGCGGCGGGGATCTCTGCGGTCGCGCCCGCCCGCAGTTTGCTTGCTCCCGCGTC
GGAGACAGTGTTTGGCTTAGGGGCAGCGGCCGCCCCGACTTCGGCCGCGCGGGTGCCTGCGG
TGGCAACGGCCGAAGTGACCGTGGAGGACGCCGAGGCATTGCCGGCTGCCGCTGGCGAACCG
GAGTCACGCGCGACGGAGCCCGATGACGACGTGGAACTGCGGCCTCGCGGCAGGTCCTTGGT
AATCATCAGCACTTTAGATGGACGAATCGCTGCACTGGATGCCGAGAATGATGGGAAAAAGC
AGTGGGATTTGGACGTGGGGTCTGGTTCCTTGGTTTCATCTAGCCTCAGCAAGCCAGAGGTG
TTTGGGAACAAGATGATCATCCCCTCCCTGGATGGAGACCTCTTCCAGTGGGACCGGGACCG
AGAGAGCATGGAGGCCGTCCCCTTCACGGTGGAGTCCCTGCTCGAATCTTCCTACAAGTTTG
GAGATGATGTTGTTCTGGTTGGAGGGAAATCTCTGATTACATACGGACTCAGTGCTTACAGT
GGAAAGCTGAGGTATATCTGTTCTGCCTTGGGATGTCGCCGATGGGATAGTGATGAAATGGA
AGAAGAGGAAGACATCTTGCTTCTGCAGCGTACGCAGAAGACTGTGCGAGCTGTCGGGCCTC
GAAGCGGCAGTGAGAAGTGGAATTTCAGTGTTGGCCACTTTGAACTTCGGTATATTCCAGAC
ATGGAAACTAGAGCCGGATTCATTGAAAGCACCTTTAAACCGGGTGGAAACAAAGAAGACTC
TAAAATTATTTCAGATGTGGAAGAACAAGAAGCCACCATGCTGGACACAGTGATAAAAGTTT
CCGTTGCTGATTGGAAGGTCATGGCGTTTAGTAGGAAGGGAGGCCGCCTGGAATGGGAGTAC
CAGTTTTGTACTCCCATCGCGTCCGCCTGGCTGGTGAGGGATGGCAAGGTCATCCCCATCAG
CCTGTTTGATGATACAAGTTACACAGCCAGCGAAGAAGCCTTGGGAGACGAAGAAGACATTG
TAGAGGCTGCTCGGGGAGCCACAGAGAACAGCGTGTACTTAGGGATGTACAGAGGCCAGCTG
TACCTGCAGTCGTCCGTCAGGGTCTCAGAAAAGTTCCCTACAAGCCCAAAGGCCTTGGAGTC
TGTAAATGGCGAAAATGCAATTATTCCTCTGCCGACGATCAAATGGAAGCCCTTAATCCATT
CTCCTTCTAGGACTCCTGTCTTGGTTGGGTCTGATGAATTTGACAAATGTCTAAGTAATGAT
AAGTATTCCCACGAAGAATACAGTAATGGTGCACTTTCAATCCTCCAGTATCCATACGATAA
CGGTTACTATCTGCCATACTACAAGAGAGAAAGGAATAAGCGGAGCACGCAGATCACAGTCA
GGTTCCTGGACAGCCCCCACTACAGCAAGAACATCCGCAAGAAGGACCCTATCCTCCTGCTG
CACTGGTGGAAGGAGATATTCGGGACGATCCTGCTTTGCATCGTAGCCACGACCTTCATCGT
GCGCAGGCTTTTCCATCCTCAGCCCCACAGGCAGCGGAAGGAGTCTGAAACTCAGTGCCAGA
CTGAAAGTAAATACGACTCCGTGAGTGCCGATGTCAGTGACAACAGCTGGAATGACATGAAG
TACTCAGGATACGTATCCCGATATCTAACAGATTTTGAGCCAATTCAGTGCATGGGTCGTGG
TGGCTTTGGCGTTGTCTTTGAAGCTAAAAACAAAGTAGATGACTGCAATTACGCTATCAAGA
GGATCCGGCTCCCCAACAGGGAGTTGGCACGGGAGAAGGTAATGCGGGAAGTTAAAGCCTTG
GCTAAGCTGGAACACCCAGGCATTGTGAGGTATTTCAACGCCTGGCTGGAAACCCCACCAGA
GAAGTGGCAAGAAGAGATGGATGAGATCTGGCTCAAAGACGAAAGCACAGACTGGCCGCTCA
GCTCCCCTAGCCCGATGGATGCCCCATCTGTTAAGATCCGAAGGATGGATCCYTTCTCTACA
AAAGAGCAGATCGAAGTCATAGCTCCTTCTCCTGAAAGAAGTCGGTCTTTCTCGGTGGGCAT
TTCCTGTGGCCAGACAAGCTCATCGGAGAGCCAGTTCTCTCCCCTGGAGTTCTCAGGGACAG
ACTGCGGAGACAACAGTGACTCAGCGGACGCAGCCTACAACCTCCAGGACAGTTGCCTGACG
GACTGCGAGGACGTGGAAGATGGCACCGTGGACGGCAATGACGAGGGACACTCCTTTGAACT
TTGTCCGTCCGAAGCTTCTCCCTATACCCGGTCTAGGGAAGGAACGTCCTCCTCCATAGTGT
TTGAGGACTCTGGCTGCGGCAACGCGTCCAGTAAGGAGGAGCCCAGAGGGAACCGGCTGCAT
GATGGCAACCATTATGTTAATAAGCTAACTGATCTCAAGTGCTCCAGCAGCAGGTCTTCTTC
AAGAACACTGTGGGCCAGCTCCAGCCCAGCTCCCCCAAGGTGTATCTGTGAAGCCACCACCT
TGTCTACCTCCCCTACCAGGCCAACCACTCTAAGCTTGGATTTCACCAACATTCAGATGCAG

FIGURE 1A(1)

```
CTGTGCAGGAAGGAGAACCTCAAAGACTGGATGAACCGGCGCTGCAGCTTGGAGGACCGGGA
GCACGGCGTGTGCCTGCACATCTTCCTGCAGATCGCAGAGGCAGTGGAGTTCCTGCACAGCA
AGGGACTCATGCACAGGGACCTCAAGCCTTCCAACATATTCTTCACAATGGATGATGTGGTC
AAGGTTGGGGACTTTGGACTGGTGACTGCTATGGACCAAGATGAAGAAGAGCAGACTGTTCT
GACTCCAATGCCAGCCTATGCTACGCACACGGGACAAGTAGGGACCAAGCTATACATGAGCC
CAGAGCAGATTCATGGAAACAACTACTCCCATAAAGTGGACATCTTCTCTTTAGGCTTGATT
CTGTTTGAACTCCTCTACCCATTCAGCACCCAGATGGAACGAGTCCGGATTTTAACTGATGT
CAGAAATCTCAAGTTTCCTCTACTGTTCACTCAGAAATATCCCCAAGAGCATATGATGGTTC
AAGACATGCTCTCTCCATCCCCCACGGAGCGGCCTGAAGCCACAGACATCATTGAAAATGCC
ATATTTGAGAACTTGGAGTTTCCCGGGAAAACGGTTCTGAGACAGCGGTCCCGCTCCATGAG
TTCATCTGGAACAAAACATTCCAGACAGCCCAGCTGCTCGTACAGCCCACTGCCTGGCAACT
AGCCCTCAGCTGCCCTCGAAGGTGGCAGAGCAGGCACCCTGAGGAACATGGCTCTCCACAGC
GGTGGACTCAGATTTTATGCTTTGATCAGTTGGACTCGGGACCAATTTTTCTAAGTCAGACT
GGATCACGGGCCTAACCCAGTTTGATCTTAACTGAACTTCAAGGAAAGGGCTGTGTAAAGGA
CACATGAACTTGTTGCTTGTCGGTGTCCCAAGACTAGCTGGTCAGCTTAGAACCTTCACTTT
TCACCAGGCGGTAGAAGAGATCCTCAAATGGTCTGAACTGGAAATGTCTTTAAAGCACAAAA
GTGTAAAAGACCCTCTCACATGGGAACTACATGTTCTAGAAACGTGCTTTCTAGAGATACAA
GGGTGATTTTGGAAGTGGTTGTTATAAAGCTGACTTCATTTTTTTCCCTGGTGAGCCGTGAC
CCATCTGCACTAATTTGCAAGGCACATAGCACAAGCTGGGTCGCCATTTATGTCGGTAGTGT
CATAGTCTGCAGCAGTGAATAGCGTCATTCTTCAGGTGGTCTAGGGAGCGCGAAAGCTTTT
TTGTACTTTTTACCTCCAATAATGGGAAAATGAAGCTTTTAGGTATTGGTCAAAAGATCTGA
TTTGAGAGTTTTGGGTTTTTTTTTTAAGTGCAGTAGGAAATGGATTATCTATTACAACTAAC
TTCTTCAATTATGGAATTTTTATCCTAGTAGAATTCTGTCTTAAATGTAATACTACAAGTGG
GTACATTCCCCCAAACTGATTATAGATAAGTTTAATCATCTCAACTTGCTAACATGTTTTCA
TTTTTCCTGTAAATACGTTTATTTTTTATTTATAAAAATTCTGAAATCAATCCATTTGGGTT
GGTGGTGTACAGAACGCACGTAAGTGTGATAACTATTATGACTTCTTTCAAGTCTAAATGAT
TTAATAAAAAATTTTAAATTAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:1)
```

FIGURE 1A(2)

MERATRPGPRALLLLLFLLLGCAAGISAVAPARSLLAPASETVFGLGAAAAPTSAARVPAVA
TAEVTVEDAEALPAAAGEPESRATEPDDDVELRPRGRSLVIISTLDGRIAALDAENDGKKQW
DLDVGSGSLVSSSLSKPEVFGNKMIIPSLDGDLFQWDRDRESMEAVPFTVESLLESSYKFGD
DVVLVGGKSLITYGLSAYSGKLRYICSALGCRRWDSDEMEEEEDILLLQRTQKTVRAVGPRS
GSEKWNFSVGHFELRYIPDMETRAGFIESTFKPGGNKEDSKIISDVEEQEATMLDTVIKVSV
ADWKVMAFSRKGGRLEWEYQFCTPIASAWLVRDGKVIPISLFDDTSYTASEEALGDEEDIVE
AARGATENSVYLGMYRGQLYLQSSVRVSEKFPTSPKALESVNGENAIIPLPTIKWKPLIHSP
SRTPVLVGSDEFDKCLSNDKYSHEEYSNGALSILQYPYDNGYYLPYYKRERNKRSTQITVRF
LDSPHYSKNIRKKDPILLLHWWKEIFGTILLCIVATTFIVRRLFHPQPHRQRKESETQCQTE
SKYDSVSADVSDNSWNDMKYSGYVSRYLTDFEPIQCMGRGGFGVVFEAKNKVDDCNYAIKRI
RLPNRELAREKVMREVKALAKLEHPGIVRYFNAWLETPPEKWQEEMDEIWLKDESTDWPLSS
PSPMDAPSVKIRRMDPFSTKEQIEVIAPSPERSRSFSVGISCGQTSSSESQFSPLEFSGTDC
GDNSDSADAAYNLQDSCLTDCEDVEDGTVDGNDEGHSFELCPSEASPYTRSREGTSSSIVFE
DSGCGNASSKEEPRGNRLHDGNHYVNKLTDLKCSSSRSSSEATTLSTSPTRPTTLSLDFTKN
TVGQLQPSSPKVYLYIQMQLCRKENLKDWMNRRCSLEDREHGVCLHIFLQIAEAVEFLHSKG
LMHRDLKPSNIFFTMDDVVKVGDFGLVTAMDQDEEEQTVLTPMPAYATHTGQVGTKLYMSPE
QIHGNNYSHKVDIFSLGLILFELLYPFSTQMERVRILTDVRNLKFPLLFTQKYPQEHMMVQD
MLSPSPTERPEATDIIENAIFENLEFPGKTVLRQRSRSMSSSGTKHSRQPSCSYSPLPGN
(SEQ ID NO:2)

FIGURE 1B

underlined = deleted in targeting construct

[ ] = sequence flanking Neo insert in targeting construct

```
CGATGTCTGCACAAGGCTGTCACTCAGGTGGCAGTGGCTGACACGTGGCCGGGCAGCTCT
GCTGCTGCGGCGCGAAGTCGAGAGGCGGCGGGGTCCGTGGCGCGCGCTCGCATTGCTCCG
AGGCTCCGAGCGGCGATACGGGCGGGCGCCGACGGCAGGGTCTCCATGCCCGCGCGTGGG
GCGGGCCGCTGATGGAGCGCGCCACCCGGCCCGGGCCGCGCGCGCTGCTGCTGCTTCTGT
TCCTGCTGCTGGGCTGCGCGGCGGGGATCTCTGCGGTCGCGCCCGCCCGCAGTTTGCTTG
CTCCCGCGTCGGAGACAGTGTTTGGCTTAGGGGCAGCGGCCGCCCCGACTTCGGCCGCGC
GGGTGCCTGCGGTGGCAACGGCCGAAGTGACCGTGGAGGACGCCGAGGCATTGCCGGCTG
CCGCTGGCGAACCGGAGTCACGCGCGACGGAGCCCGATGACGACGTGGAACTGCGGCCTC
GCGGCAGGTCCTTGGTAATCATCAGCACTTTAGATGGACGAATCGCTGCACTGGATGCCG
AGAATGATGGGAAAAAGCAGTGGGATTTGGACGTGGGGTCTGGTTCCTTGGTTTCATCTA
GCCTCAGCAAGCCAGAGGTGTTTGGGAACAAGATGATCATCCCCTCCCTGGATGGAGACC
TCTTCCAGTGGGACCGGGACCGAGAGAGCATGGAGGCCGTCCCCTTCACGGTGGAGTCCC
TGCTCGAATCTTCCTACAAGTTTGGAGATGATGTTGTTCTGGTTGGAGGGAAATCTCTGA
TTACATACGGACTCAGTGCTTACAGTGGAAAGCTGAGGTATATCTGTTCTGCCTTGGGAT
GTCGCCGATGGGATAGTGATGAAATGGAAGAAGAGGAAGACATCTTGCTTCTGCAGCGTA
CGCAGAAGACTGTGCGAGCTGTCGGGCCTCGAAGCGGCAGTGAGAAGTGGAATTTCAGTG
TTGGCCACTTTGAACTTCGGTATATTCCAGACATGGAAACTAGAGCCGGATTCATTGAAA
GCACCTTTAAACCGGGTGGAAACAAAGAAGACTCTAAAATTATTTCAGATGTGGAAGAAC
AAGAAGCCACCATGCTGGACACAGTGATAAAAGTTTCCGTTGCTGATTGGAAGGTCATGG
CGTTTAGTAGGAAGGGAGGCCGCCTGGAATGGGAGTACCAGTTTTGTACTCCCATCGCGT
CCGCCTGGCTGGTGAGGGATGGCAAGGTCATCCCCATCAGCCTGTTTGATGATACAAGTT
ACACAGCCAGCGAAGAAGCCTTGGGAGACGAAGAAGACATTGTAGAGGCTGCTCGGGGAG
CCACAGAGAACAGCGTGTACTTAGGGATGTACAGAGGCCAGCTGTACCTGCAGTCGTCCG
TCAGGGTCTCAGAAAAGTTCCCTACAAGCCCAAAGGCCTTGGAGTCTGTAAATGGCGAAA
ATGCAATTATTCCTCTGCCGACGATCAAATGGAAGCCCTTAATCCATTCTCCTTCTAGGA
CTCCTGTCTTGGTTGGGTCTGATGAATTTGACAAATGTCTAAGTAATGATAAGTATTCCC
ACGAAGAATACAGTAATGGTGCACTTTCAATCCTCCAGTATCCATACGATAACGGTTACT
ATCTGCCATACTACAAGAGAGAAAGGAATAAGCGGAGCACGCAGATCACAGTCAGGTTCC
TGGACAGCCCCCACTACAGCAAGAACATCCGCAAGAAGGACCCTATCCTCCTGCTGCACT
GGTGGAAGGAGATATTCGGGACGATCCTGCTTTGCATCGTAGCCACGACCTTCATCGTGC
GCAGGCTTTTCCATCCTCAGCCCCACAGGCAGCGGAAGGAGTCTGAAACTCAGTGCCAGA
CTGAAAGTAAATACGACTCCGTGAGTGCCGATGTCAGTGACAACAGCTGGAATGACATGA
AGTACTCAGGATACGTATCCCGATATCTAACAGATTTTGAGCCAATTCAGTGCATGGGTC
GTGGTGGCTTTGGCGTTGTCTTTGAAGCTAAAAACAAAGTAGATGACTGCAATTACGCTA
TCAAGAGGATCCGGCTCCCCAACAGGGAGTTGGCACGGGAGAAGGTAATGCGGGAAGTTA
AAGCCTTGGCTAAGCTGGAACACCCAGGCATTGTGAGGTATTTCAACGCCTGGCTGGAAA
CCCCACCAGAGAAGTGGCAAGAAGAGATGGATGAGATCTGGCTCAAAGACGAAAGCACAG
ACTGGCCGCTCAGCTCCCCTAGCCCGATGGATGCCCCATCTGTTAAGATCCGAAGGATGG
ATCCYTTCTCTACAAAAGAGCAGATCGAAGTCATAGCTCCTTCTCCTGAAAGAAGTCGGT
CTTTCTCGGTGGGCATTTCCTGTGGCCAGACAAGCTCATCGGAGAGCCAGTTCTCTCCCC
TGGAGTTCTCAGGGACAGACTGCGGAGACAACAGTGACTCAGCGGACGCAGCCTACAACC
TCCAGGACAGTTGCCTGACGGACTGCGAGGACGTGGAAGATGGCACCGTGGACGGCAATG
ACGAGGGACACTCCTTTGAACTTTGTCCGTCCGAAGCTTCTCCC [TATACCCGGTCTAGG
```

FIGURE 2A(1)

GAAGCAACGTCCTCCTCCATAGTGTTTGAGGACTCTGGCTGCGGCAACGCGTCCAGTAAG
GAGGAGCCCAGAGGGAACCGGCTGCATGATGGCAACCATTATGTTAATAAGCTAACTGAT
CTCAAGTGCTCCAGCAGCAGGTCTTCTTCAGAAGCCACCACCTTGTCTACCTCCCCTACC
AGGCCAACCACTCTAAGCTTGGATTTCACCAAGAACACTGTGGGCCAGCTCCAGCCCAGC
TCCCCCAAGGTGTATCTGTACATTCAGATGCAGCTGTGCAGGAAGGAGAACCTC] <u>AAAGA</u>
<u>CTGGATGAACCGGCGCTGCAGCTTGGAGGACCGGGAGCACGGCGTGTGCCTGCACATCTT</u>
<u>CCTGCAGATCGCAGAGGCAGTGGAGTTCCTGCAC</u> [AGCAAGGGACTCATGCACAGGGACC
TCAAG] CCTTCCAACATATTCTTCACAATGGATGATGTGGTCAAGGTTGGGGACTTTGGA
CTGGTGACTGCTATGGACCAAGATGAAGAAGAGCAGACTGTTCTGACTCCAATGCCAGCC
TATGCTACGCACACGGCACAAGTAGGGACCAAGCTATACATGAGCCCAGAGCAGATTCAT
GGAAACAACTACTCCCATAAAGTGGACATCTTCTCTTTAGGCTTGATTCTGTTTGAACTC
CTCTACCCATTCAGCACCCAGATGGAACGAGTCCGGATTTTAACTGATGTCAGAAATCTC
AAGTTTCCTCTACTGTTCACTCAGAAATATCCCCAAGAGCATATGATGGTTCAAGACATG
CTCTCTCCATCCCCCACGGAGCGGCCTGAAGCCACAGACATCATTGAAAATGCCATATTT
GAGAACTTGGAGTTTCCCGGGAAAACGGTTCTGAGACAGCGGTCCCGCTCCATGAGTTCA
TCTGGAACAAAACATTCCAGACAGCCCAGCTGCTCGTACAGCCCACTGCCTGGCAACTAG
CCCTCAGCTGCCCTCGAAGGTGGCAGAGCAGGCACCCTGAGGAACATGGCTCTCCACAGC
GGTGGACTCAGATTTTATGCTTTGATCAGTTGGACTCGGGACCAATTTTTCTAAGTCAGA
CTGGATCACGGGCCTAACCCAGTTTGATCTTAACTGAACTTCAAGGAAAGGGCTGTGTAA
AGGACACATGAACTTGTTGCTTGTCGGTGTCCCAAGACTAGCTGGTCAGCTTAGAACCTT
CACTTTTCACCAGGCGGTAGAAGAGATCCTCAAATGGTCTGAACTGGAAATGTCTTTAAA
GCACAAAAGTGTAAAAGACCCTCTCACATGGGAACTACATGTTCTAGAAACGTGCTTTCT
AGAGATACAAGGGTGATTTTGGAAGTGGTTGTTATAAAGCTGACTTCATTTTTTTCCCTG
GTGAGCCGTGACCCATCTGCACTAATTTGCAAGGCACATAGCACAAGCTGGGTCGCCATT
TATGTCGGTAGTGTCATAGTCTGCAGCAGTGAATAGCGTCATTCTTCAGGTGGTCTAGGG
AGCGCGAAAAGCTTTTTTGTACTTTTTACCTCCAATAATCGGAAAATGAAGCTTTTAGGT
ATTGGTCAAAAGATCTGATTTGAGAGTTTTGGGTTTTTTTTTAAGTGCAGTAGGAAATG
GATTATCTATTACAACTAACTTCTTCAATTATGGAATTTTTATCCTAGTAGAATTCTGTC
TTAAATGTAATACTACAAGTGGGTACATTCCCCCAAACTGATTATAGATAAGTTTAATCA
TCTCAACTTGCTAACATGTTTTCATTTTTCCTGTAAATACGTTTATTTTTTATTTATAAA
AATTCTGAAATCAATCCATTTGGGTTGGTGGTGTACAGAACGCACGTAAGTGTGATAACT
ATTATGACTTCTTTCAAGTCTAAATGATTTAATAAAAAAATTTTAAATTAAAAAAAAAAA
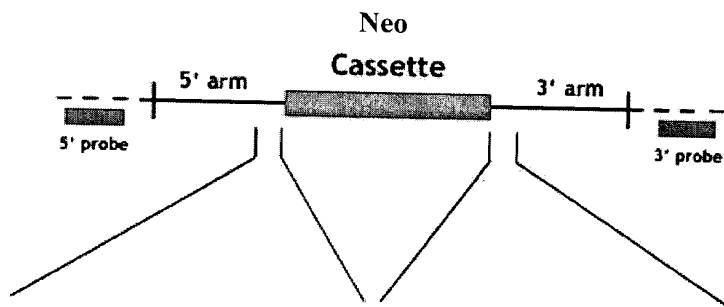AAAAAAAAAAAAA

FIGURE 2A(2)

Gene Sequence
Structure *

2874 bp   Sequence Deleted   2972 bp

Size of full-length
cDNA: 4510 bp

Targeting Vector*
(genomic sequence)

Neo
Cassette

5' arm   3' arm

5' probe   3' probe

Arm Length:
5': 2.4 kb
3': 1.3 kb

———— Targeting Vector
- - - - - Endogenous Locus

* Not drawn to scale

5'>ACCATTATGTTAATAAGCTAA
CTGATCTCAAGTGCTCCAGCAGCA
GGTCTTCTTCAGAAGCCACCACCT
TGTCTACCTCCCCTACCAGGCCAA
CCACTCTAAGCTTGGATTTCACCA
AGAACACTGTGGGCCAGCTCCAGC
CCAGCTCCCCCAAGGTGTATCTGT
ACATTCAGATGCAGCTGTGCAGGA
AGGAGAACCTC<3' (SEQ ID
NO:3)

5'>AGCAAGGGACTCATGCACGGG
ACCTCAAGGTCTGTAGCCAGAGGC
GGCCACGCCGGGCTTTGGGTGTGC
CCTGGGGTTCAGAGCAGAGGTCGG
GGAAGGAAGCAGGGAAGGAAGAAG
TCTCATATGTGAAAGGCTCAGGCA
GACTGTGCATCTTCCTTTACGGCC
TGTTTATTTTTGTTTTACTGTAAA
CACTGTTTCCA<3' (SEQ ID
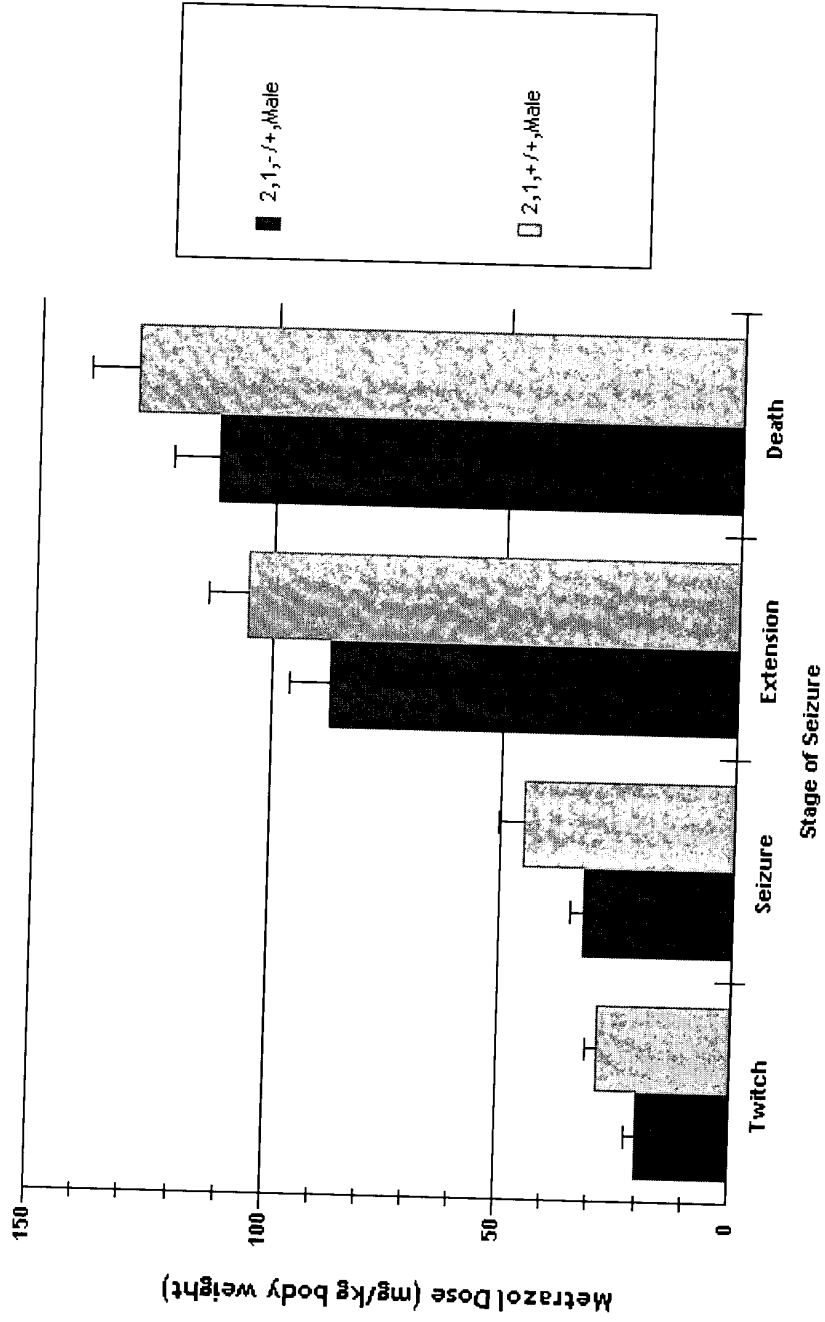NO:4)

FIGURE 2B

Phenotypic Data Summary - Metrazol

FIGURE 3